Application of Ab-Initio Quantum and Classical Molecular Dynamics Simulations to Study Clustered DNA Damage

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The enhanced biological effectiveness of high linear-energy-transfer (LET) radiation is generally attributed to a higher frequency of clustered DNA damage; however, the chemical properties of clustered damaged that increase the potential for induction of biological effects, such as mutations and cell death, are largely unknown. As a step toward filling this knowledge gap, we have investigated the structure and energetics of lesions in close proximity on duplex DNA. Quantum calculations were used to model the changes in structure, hydrogen bonding, stacking properties, and electrostatic potential induced by oxidized bases and abasic sites. Thermodynamic integration based on molecular dynamics simulations with classical force fields was used to calculate perturbations of duplex DNA stability due to single and multiple lesions. Quantum models, classical free energy calculations, and experimental data were in reasonable agreement for the amount of DNA destabilization induced by an isolated 8-oxoguanine lesion or abasic site. Two lesions were considered to be chemically independent if their effects on the free energy of duplex destabilization were additive. We estimated the minimum separation required for chemical isolation by systematically changing the position of lesions on a 12-basepair oligonucleotide. The minimum separation of chemically independent 8-oxoguanine lesions was less than the DNA footprint of OGG1 (Burner et al. 2000), the enzyme in the base excision repair pathway that removes 8-oxoguanine from DNA. Hence, the properties of isolated 8-oxoguanine lesions can be used to model multi-lesion substrates of OGG1. Comparison of our results to models for the induction of clustered DNA damage (Nikjoo et al. 1997) can provide an estimate of the probability that radiation with a specified LET will induce lesions sufficiently close to have strong chemical interactions. In this presentation, we will describe our computational methods and present results relevant to the induction of clustered damage by high- and low-LET radiations.

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